CHRONIC TOXICITY SUMMARY

FORMALDEHYDE

(methanal; oxoymethane; oxomethylene; methylene oxide; formic aldehyde; methyl aldehyde)

CAS Registry Number: 50-00-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**3 μg/m^3 (2 ppb)**
Critical effect(s)	Upper and lower airway irritation and eye irritation in humans; degenerative, inflammatory and hyperplastic changes of the nasal mucosa in humans and animals
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1994; CRC, 1994)

Description	Colorless gas
Molecular formula	CH_2O
Molecular weight	30.03 g/mol
Density	0.815 g/L @ -20°C
Boiling point	-19.1°C
Melting point	-92°C
Vapor pressure	220 kPa @ 0°C
Solubility	Soluble in water, ethanol, ether, acetone
Conversion factor	1 ppm = 1.23-1.25 mg/m^3 @ 25° C

III. Major Uses or Sources (CARB, 1992; HSDB, 1995)

Formaldehyde is used in the manufacture of melamine, polyacetal, and phenolic resins. Phenol-formaldehyde resins are used in the production of plywood, particleboard, foam insulation, and a wide variety of molded or extruded plastic items. Formaldehyde is also used as a preservative, a hardening and reducing agent, a corrosion inhibitor, a sterilizing agent, and in embalming fluids. Indoor sources include upholstery, permanent press fabrics, carpets, pesticide formulations, and cardboard and paper products. Outdoor sources include emissions from fuel combustion (motor vehicles), industrial fuel combustion (power generators), oil refining processes, and other uses (copper plating, incinerators, etc.). In 1997, the population-weighted annual average exposure in the South Coast Air Basin was estimated (using a model calibrated against actual atmospheric measurements) to be 4.7 ppb formaldehye (CARB, 1999a). The annual statewide industrial

emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1,589,810 pounds of formaldehyde (CARB, 1999b).

IV. Effects of Human Exposure

Formaldehyde primarily affects the mucous membranes of the upper airways and eyes. Exposed populations that have been studied include embalmers, residents in houses insulated with urea-formaldehyde foam, anatomy class students, histology technicians, wood and pulpmill workers, and asthmatics. The voluminous body of data describing these effects has been briefly summarized below. For the sake of brevity, only the studies that best represent the given effects are presented.

Kerfoot and Mooney (1975) reported that estimated formaldehyde exposures of 0.25-1.39 ppm evoked numerous complaints of upper respiratory tract and eye irritation among 7 embalmers at 6 different funeral homes. Three of the 7 embalmers in this study reportedly had asthma. Levine *et al.* (1984) examined the death certificates of 1477 Ontario undertakers. Exposure measurements taken from a group of West Virginia embalmers were used as exposure estimates for the embalming process, ranging from 0.3-0.9 ppm (average 1-hour exposure) and 0.4-2.1 ppm (peak 30-minute exposure). Mortality due to non-malignant diseases was significantly elevated due to a two-fold excess of deaths related to the digestive system. The authors suggest increased alcoholism could have contributed to this increase.

Ritchie and Lehnen (1987) reported a dose-dependent increase in health complaints (eye and throat irritation, and headaches) in 2000 residents living in 397 mobile and 494 conventional homes, that was demonstrated by logistic regression. Complaints of symptoms of irritation were noted at concentrations of 0.1 ppm formaldehyde or above. Similarly, Liu *et al.* (1991) found that exposure to 0.09 ppm (0.135 mg/m^3) formaldehyde exacerbated chronic respiratory and allergy problems in residents living in mobile homes.

Employees of mobile day-care centers (66 subjects) reported increased incidence of eye, nose and throat irritation, unnatural thirst, headaches, abnormal tiredness, menstrual disorders, and increased use of analgesics as compared to control workers (Olsen and Dossing, 1982). The mean formaldehyde concentration in these mobile units was 0.29 ppm (0.43 mg/m^3) (range = 0.24 - 0.55 mg/m^3). The exposed workers were exposed in these units a minimum of 3 months. A control group of 26 subjects in different institutions was exposed to a mean concentration of 0.05 ppm (0.08 mg/m^3) formaldehyde.

Occupants of houses insulated with urea-formaldehyde foam insulation (UFFI) (1726 subjects) were compared with control subjects (720 subjects) for subjective measures of irritation, pulmonary function (FVC, FEV_1, FEF_{25-75}, FEF_{50}), nasal airway resistance, odor threshold for pyridine, nasal cytology, and hypersensitivity skin-patch testing (Broder *et al.*, 1988). The mean length of time of exposure to UFFI was 4.6 years. The mean concentration of formaldehyde in the UFFI-exposed group was 0.043 ppm, compared with 0.035 ppm for the controls. A significant increase in symptoms of eye, nose and throat irritation was observed in subjects from UFFI homes, compared with controls. No other differences from control measurements were observed.

An increase in severity of nasal epithelial histological lesions, including loss of cilia and goblet cell hyperplasia (11%), squamous metaplasia (78%), and mild dysplasia (8%), was observed in 75 wood products workers exposed to between 0.1 and 1.1 mg/m^3 formaldehyde for a mean duration of 10.5 years (range = 1 - 39 years), compared to an equal number of control subjects (Edling *et al.*, 1988). Only three exposed men had normal mucosa. A high frequency of symptoms relating to the eyes and upper airways was reported in exposed workers. Nasal symptoms included mostly a runny nose and crusting. The histological grading showed a significantly higher score for nasal lesions when compared with the referents (2.9 versus 1.8). Exposed smokers had a higher, but non-significant, score than ex-smokers and non-smokers. When relating the histological score to duration of exposure, the mean histological score was about the same regardless of years of employment. In addition, no difference in the histological scores was found between workers exposed only to formaldehyde and those exposed to formaldehyde and wood dust.

Alexandersson and Hedenstierna (1989) evaluated symptoms of irritation, spirometry, and immunoglobulin levels in 34 wood workers exposed to formaldehyde over a 4-year period. Exposure to 0.4 - 0.5 ppm formaldehyde resulted in significant decreases in FVC, FEV_1, and FEF_{25-75}. Removal from exposure for 4 weeks allowed for normalization of lung function in the non-smokers.

Kriebel *et al.* (1993) conducted a subchronic epidemiological study of 24 anatomy class students exposed to a range of formaldehyde of 0.49 to 0.93 ppm (geometric mean = 0.73 $\pm$ 1.22 ppm) for 3 hours per week for 10 weeks. One subject was a smoker, 2 reported current asthma, and 3 reported childhood asthma without current symptoms. Eye and throat irritation was significantly elevated in the students after classes compared with pre-laboratory session exposures. In addition, peak expiratory flow measurements declined by an average of 10 L/minute (2% of baseline), but returned to normal after 14 weeks of non-exposure.

Histology technicians (280 subjects) were shown to have reduced pulmonary function, as measured by FVC, FEV_1, FEF_{25-75}, and FEF_{75-85}, compared with 486 controls (Kilburn *et al.*, 1989). The range of formaldehyde concentrations was 0.2 - 1.9 ppm, volatilized from formalin preservative solution.

Malaka and Kodama (1990) investigated the effects of formaldehyde exposure in plywood workers (93 exposed, 93 controls) exposed for 26.6 years, on average, to 1.13 ppm (range = 0.28 - 3.48 ppm). Fifty-three smokers were present in both study groups. Exposure assessment was divided into 3 categories: high (> 5 ppm), low (< 5 ppm), and none (reference group). Subjective irritation and pulmonary function tests were performed on each subject, and chest x-rays were taken of 10 randomly selected volunteers from each group. Respiratory symptoms of irritation were found to be significantly increased in exposed individuals, compared with controls. In addition, exposed individuals exhibited significantly reduced FEV_1, FEV_1/FVC, and $FEF_{25-75,}$ compared with controls. Forced vital capacity was not significantly reduced. Pulmonary function was not found to be different after a work shift, compared to the same measurement taken before the shift. No differences in chest x-rays were observed between exposed and control workers.

Occupational exposure to formaldehyde concentrations estimated to be 0.025 ppm (0.038 mg/m^3) for greater than 6 years resulted in complaints by 22 exposed workers of respiratory, gastrointestinal, musculoskeletal, and cardiovascular problems, and in elevated formic acid excretion in the urine (Srivastava *et al.*, 1992). A control group of 27 workers unexposed to formaldehyde was used for comparison. A significantly higher incidence of abnormal chest x-rays was also observed in formaldehyde-exposed workers compared with controls.

Chemical plant workers (70 subjects) were exposed to a mean of 0.17 ppm (0.26 mg/m^3) formaldehyde for an unspecified duration (Holmstrom and Wilhelmsson, 1988). Compared with 36 control workers not exposed to formaldehyde, the exposed subjects exhibited a higher frequency of eye, nose, and deep airway discomfort. In addition, the exposed subjects had diminished olfactory ability, delayed mucociliary clearance, and decreased FVC.

Alexandersson *et al.* (1982) compared the irritant symptoms and pulmonary function of 47 carpentry workers exposed to a mean concentration of formaldehyde of 0.36 ppm (range = 0.04 - 1.25 ppm) with 20 unexposed controls. The average length of employment for the exposed workers was 5.9 years. Symptoms of eye and throat irritation as well as airway obstruction were more common in exposed workers. In addition, a significant reduction in FEV_1, FEV_1/FVC, and MMF was observed in exposed workers, as compared with controls.

Horvath *et al.* (1988) compared subjective irritation and pulmonary function in 109 workers exposed to formaldehyde with similar measures in a control group of 254 subjects. The formaldehyde concentrations for the exposed and control groups were 0.69 ppm (1.04 mg/m^3) and 0.05 ppm (0.08 mg/m^3), respectively. Mean formaldehyde concentration in the pre-shift testing facility and the state (Wisconsin) ambient outdoor - formaldehyde level were both 0.04 ppm (0.06 mg/m^3). Duration of formaldehyde exposure was not stated. Subjects were evaluated pre- and post work-shift and compared with control subjects. Significant differences in symptoms of irritation, FEV_1, FEV_1/FVC ratio, FEF_{50}, FEF_{25}, and FEF_{75} were found when comparing exposed subjects' pre- and post work-shift values. However, the pre-workshift values were not different from controls.

The binding of formaldehyde to endogenous proteins creates haptens that can elicit an immune response. Chronic exposure to formaldehyde has been associated with immunological hypersensitivity as measured by elevated circulating IgG and IgE autoantibodies to human serum albumin (Thrasher *et al.*, 1987). In addition, a decrease in the proportion of T-cells was observed, indicating altered immunity. Thrasher *et al.* (1990) later found that long-term exposure to formaldehyde was associated with autoantibodies, immune activation, and formaldehyde-albumin adducts in patients occupationally exposed, or residents of mobile homes or of homes containing particleboard sub-flooring. The authors suggest that the hypersensitivity induced by formaldehyde may account for a mechanism for asthma and other health complaints associated with formaldehyde exposure.

Symptoms of irritation were reported by 66 workers exposed for 1 - 36 years (mean = 10 years) to a mean concentration of 0.17 ppm (0.26 mg/m^3) formaldehyde (Wilhelmsson and Holmstrom,

1992). Controls (36 subjects) consisted of office workers in a government office and were exposed to a mean concentration of 0.06 ppm (0.09 mg/m^3) formaldehyde. The significant increase in symptoms of irritation in exposed workers did not correlate with total serum IgE antibody levels. However, 2 exposed workers, who complained of nasal discomfort, had elevated IgE levels. In another occupational health study, 37 workers, who were exposed for an unspecified duration to formaldehyde concentrations in the range of 0.003 to 0.073 ppm, reported ocular irritation; however, no significant serum levels of IgE or IgG antibodies to formaldehyde-human serum albumin were detected (Grammer *et al.*, 1990).

An epidemiological study of the effects of formaldehyde on 367 textile and shoe manufacturing workers employed for a mean duration of 12 years showed no significant association between formaldehyde exposure, pulmonary function (FVC, FEV_1, and PEF) in normal or asthmatic workers, and occurrence of specific IgE antibodies to formaldehyde (Gorski and Krakowiak, 1991). The concentrations of formaldehyde did not exceed 0.5 ppm (0.75 mg/m^3).

Workers (38 total) exposed for a mean duration of 7.8 years to 0.11 - 2.12 ppm (mean = 0.33 ppm) formaldehyde were studied for their symptomatology, lung function, and total IgG and IgE levels in the serum (Alexandersson and Hedenstierna, 1988). The control group consisted of 18 unexposed individuals. Significant decrements in pulmonary function (FVC and FEV_1) were observed, compared with the controls. Eye, nose, and throat irritation was also reported more frequently by the exposed group, compared with the control group. No correlation was found between duration of exposure, or formaldehyde concentration, and the presence of IgE and IgG antibodies.

The effects of formaldehyde on asthmatics appears to be dependent on previous, repeated exposure to formaldehyde. Burge *et al.* (1985) found that 3 out of 15 occupationally exposed workers challenged with formaldehyde vapors at concentrations from 1.5 ppm to 20.6 ppm for brief duration exhibited late asthmatic reactions. Six other subjects had immediate asthmatic reactions likely due to irritant effects. Asthmatic responses (decreased PEF, FVC, and FEV_1) were observed in 12 occupationally-exposed workers challenged with 1.67 ppm (2.5 mg/m^3) formaldehyde (Nordman *et al.*, 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde vapors (concentration not measured) (Hendrick and Lane, 1977). In asthmatics not occupationally exposed to formaldehyde, Sheppard *et al.* (1984) found that a 10-minute challenge with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in airway resistance or thoracic gas volume.

V. Effects of Animal Exposure

Fischer-344 rats and B6C3F1 mice (120 animals/sex) were exposed to concentrations of 0, 2.0, 5.6, or 14.3 ppm formaldehyde vapor for 6 hours/day, 5 days/week for 24 months (Kerns *et al.*, 1983). The exposure period was followed by up to 6 months of non-exposure. Interim sacrifices were conducted at 6, 12, 18, 24, 27, and 30 months. Both male and female rats in the 5.6 and 14.3 ppm groups demonstrated decreased body weights over the 2-year period. At the 6 month sacrifice, the rats exposed to 14.3 ppm formaldehyde had non-neoplastic lesions of epithelial

dysplasia in the nasal septum and turbinates. As the study progressed, epithelial dysplasia, squamous dysplasia, and mucopurulent rhinitis increased in severity and distribution in all exposure groups. In mice, cumulative survival decreased in males from 6 months to the end of the study. Serous rhinitis was detected at 6 months in the 14.3 ppm group of mice. Metaplastic and dysplastic changes were noted at 18 months in most rats in the 14.3 ppm group and in a few mice in the 5.6 ppm exposure group. By 24-months, the majority of mice in the 14.3 ppm group had metaplastic and dysplastic changes associated with serous rhinitis, in contrast to a few mice in the 5.6 ppm group and a few in the 2 ppm group (exact number not given).

Woutersen *et al*. (1989) exposed male Wistar rats (60 animals/group) 6 hr/day for 5 days/week to 0, 0.1, 1.0 and 10 ppm formaldehyde vapor for 28 months. Compound-related nasal lesions of the respiratory and olfactory epithelium were observed only in the 10 ppm group. In the respiratory epiethlium, the lesions consisted of rhinitis, squamous metaplasia and basal cell/pseudoepithelial hyperplasia. In the olfactory region, the lesions included epithelial degeneration and rhinitis. No differences in behavior or mortality were noted among the various groups. However, growth retardation was observed in the 10 ppm group from day 14 onwards. In a parallel study, male Wistar rats were exposed to 0, 0.1, 1.0 and 10 ppm formaldehyde for 3 months followed by a 25-month observation period. Compound-related histopathological changes were found only in the noses of the 10 ppm group and comprised of increased incidences of squamous metaplasia of the respiratory epithelium and rhinitis.

In a chronic exposure study that primarily investigated aspects of nasal tumor development, Monticello *et al*. (1996) examined nasal cavities of male F-344 rats (0 - 10 ppm, 90 animals/group; 15 ppm, 147 animals) following exposure to 0, 0.7, 2, 6, 10, and 15 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months. Treatment-related decreases in survival were apparent only in the 15 ppm group. Nasal lesions at the two highest doses included epithelial hypertrophy and hyperplasia, squamous metaplasia, and a mixed inflammatory cell infiltrate. Lesions in the 6 ppm group were minimal to absent and limited to focal squamous metaplasia in the anterior regions of the nasal cavity. No formaldehyde-induced lesions were observed in the 0.7 or 2 ppm groups.

Kamata *et al*. (1997) exposed 32 male F-344 rats/group to gaseous formaldehyde at 0, 0.3, 2, and 15 ppm 6 hr/day, 5 days/week for up to 28 weeks. A room control, non-exposed group was also included in the study. Five animals per group were randomly selected at the end of the 12^{th}, 18^{th}, and 24^{th} months, and surviving animals at 28 months were sacrificed for full pathological evaulation. Behavioural effects related to sensory irritation were evident in the 15 ppm group. Significant decreases in food consumption, body weight and survival were also evident in this group. No exposure-related hematological findings were observed. Biochemical and organ weight examination revealed decreased triglyceride levels and absolute liver weights at the highest exposure, but was likely related to reduced food consumption. Abnormal histopathological findings were confined to the nasal cavity. Inflammatory cell infiltration, erosion or edema of the nasal cavity was evident in all groups, including controls. Significantly increased incidence of non-proliferative (squamous cell metaplasia without epithelial cell hyperplasia) and proliferative lesions (epithelial cell hyperplasia with squamous cell metaplasia) were observed in the nasal cavities beginning at 2 ppm. In the 0.3 ppm group, a non-significant

increase in proliferative nasal lesions (4/20 animals) were observed in rats that were either sacrificed or died following the 18th month of exposure.

Rusch *et al.* (1983) exposed groups of 6 male cynomolgus monkeys, 20 male or female rats, and 10 male or female hamsters to 0, 0.2, 1.0, or 3.0 ppm (0, 0.24, 1.2, or 3.7 mg/m^3) formaldehyde vapor for 22 hours/day, 7 days/week for 26 weeks. There was no treatment-related mortality during the study. In monkeys, the most significant findings were hoarseness, congestion and squamous metaplasia of the nasal turbinates in 6/6 monkeys exposed to 2.95 ppm. There were no signs of toxicity in the lower exposure groups. In the rat, squamous metaplasia and basal cell hyperplasia of the nasal epithelia were significantly increased in rats exposed to 2.95 ppm. The same group exhibited decreased body weights and decreased liver weights. In contrast to monkeys and rats, hamsters did not show any signs of response to exposure, even at 2.95 ppm.

Kimbell et al. (1997) exposed male F-344 rats ($\leq$ 6/group) to 0, 0.7, 2, 6, 10, and 15 ppm 6 hr/day, 5 days/week for 6 months. Squamous metaplasia was not observed in any regions of the nasal cavity in any of the control, 0.7, or 2 ppm groups. However, the extent and incidence of squamous metaplasia in the nasal cavity increased with increasing dose beginning at 6 ppm.

In subchronic studies, Wilmer *et al.* (1989) found that intermittent (8 hours/day, 5 days/week) exposures of rats to 4 ppm formaldehyde for 13 weeks resulted in significant histological changes in the nasal septum and turbinates. In contrast, continuous exposure of rats for 13 weeks to 2 ppm formaldehyde did not produce significant lesions. This study revealed the concentration dependent nature of the nasal lesions caused by formaldehyde exposure. Zwart *et al.*, (1988) exposed male and female Wistar rats (50 animals/group/sex) to 0, 0.3, 1, and 3 ppm formaldehyde vapor for 6 hr/day, 5 days/week for 13 weeks. Compound related histopathological nasal changes varying from epithelial disarrangement to epithelial hyperplasia and squamous metaplasia were found in the 3 ppm group, and were restricted to a small area of the anterior respiratory epithelium. These changes were confirmed by electron microscopy and were not observed in other groups. Wouterson *et al.* (1987) exposed rats (20 per group) to 0, 1, 10, or 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks. Rats exposed to 20 ppm displayed retarded growth, yellowing of the fur, and significant histological lesions in the respiratory epithelium. Exposure to 10 ppm did not affect growth, but resulted in significant histological lesions in the respiratory tract. No effects on specific organ weights, blood chemistries, liver glutathione levels, or urinalysis were detected at any level. No significant adverse effects were seen at the 1.0 ppm exposure level.

Appelman *et al.* (1988) found significant nasal lesions in rats (20 per group; 0, 0.1, 1.0, or 10.0 ppm) exposed to 10 ppm formaldehyde 6 hours/day, 5 days/week for 52 weeks, but exposure to 1.0 ppm or less for this period did not result in nasal histological lesions. However, the rats exposed to formaldehyde displayed decreased body weight in all groups compared with controls.

Apfelbach and Weiler (1991) determined that rats (5 exposed, 10 controls) exposed to 0.25 ppm (0.38 mg/m^3) formaldehyde for 130 days lost the olfactory ability to detect ethyl acetate odor.

Maronpot *et al.* (1986) exposed groups of 20 mice to 0, 2, 4, 10, 20, or 40 ppm formaldehyde 6 hours/day, 5 days/week, for 13 weeks. Histological lesions in the upper respiratory epithelium were seen in animals exposed to 10 ppm or greater. Exposure to 40 ppm was lethal to the mice.

A six-month exposure of rats to 0, 0.5, 3, and 15 ppm formaldehyde (3 rats per group) resulted in significantly elevated total lung cytochrome P450 in all formaldehyde-exposed groups (Dallas *et al.*, 1989). The degree of P450 induction was highest after 4 days exposure and decreased slightly over the course of the experiment.

A developmental toxicity study on formaldehyde was conducted by Martin (1990). Pregnant rats (25 per group) were exposed to 0, 2, 5, or 10 ppm formaldehyde for 6 hours/day, during days 6-15 of gestation. Although exposure to 10 ppm formaldehyde resulted in reduced food consumption and body weight gain in the maternal rats, no effects on the number, viability or normal development of the fetuses were seen. In addition, Saillenfait *et al.* (1989) exposed pregnant rats (25 per group) to 0, 5, 10, 20, or 40 ppm formaldehyde from days 6 - 20 of gestation. Maternal weight gain and fetal weight were significantly reduced in the 40 ppm exposure group. No significant fetotoxicity or teratogenic defects were observed.

VI. Derivation of Chronic Reference Exposure Level (REL)

Studies	Wilhelmsson and Holmstrom, 1992; supported by Edling *et al*., 1988
Study population	Human chemical plant workers (66 subjects)
Exposure method	Discontinuous occupational exposure
Critical effects	Nasal and eye irritation, nasal obstruction, and lower airway discomfort; histopathological nasal lesions including rhinitis, squamous metaplasia, and dysplasia
LOAEL	Mean of 0.26 mg/m^3 (range = 0.05 to 0.6 mg/m^3) (described as exposed group)
NOAEL	Mean of 0.09 mg/m^3 (described for control group of office workers)
Exposure continuity	8 hours/day, 5 days/week (assumed)
Exposure duration	10 years (average); range = 1-36 years
Average occupational concentration	0.032 mg/m^3 for NOAEL group (0.09 x 10/20 x 5/7)
Human equivalent concentration	0.032 mg/m^3
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference level	0.003 mg/m^3 (3 $\mu g/m^3$; 0.002 ppm; 2 ppb)

The Wilhelmsson and Holmstrom (1992) study was selected because it was a human occupational study that contained a LOAEL and a NOAEL, was recent, and contained a

reasonable number of subjects. The supporting occupational study by Edling *et al*. (1988) noted similar sensory irritation results due to long-term formaldehyde exposure. In addition, nasal biopsies from exposed workers in the Edling *et al*. (1988) study exhibited nasal epithelial lesions similar to those found in subchronic and chronic animal studies.

For comparison with the proposed REL of 3 $\mu g/m^3$, we estimated a REL from Edling *et al*. (1988). A median concentration of 0.6 mg/m^3 was determined for the LOAEL from the TWA range of 0.1-1.1 mg/m^3. A NOAEL was not reported. The average continuous occupational concentration was 0.2 mg/m^3 (0.6 x 10/20 x 5/7) and the exposure duration was 10.5 years (range = 1 – 39 years). Application of a UF of 10 for intraspecies variability and a UF of 10 for estimation of a NOAEL from the LOAEL would result in a REL of 2 $\mu g/m^3$ (2 ppb).

Table 1 presents a summary of potential RELs based on chronic and subchronic animal studies. The toxicological endpoint was nasal lesions, consisting principally of rhinitis, squamous metaplasia, and dyplasia of the respiratory epithelium.

Table 1. Summary of Chronic and Subchronic Formaldehyde Studies in Experimental Animals

Study	*Animal*	Exposure Duration	LOAEL/ NOAEL (mg/m^3)	HEC adj. (mg/m^3)	Cumulative UF	REL ($\mu g/m^3$)
Woutersen *et al*., 1989	rat	28 mo	9.8 / 1.0	0.06	30	2
Kerns *et al*., 1983	rat	24 mo	2.0 / NA	0.1	300	0.3
Monticello *et al*., 1996	rat	24 mo	6.01 / 2.05	0.1	30	4
Kamata *et al*., 1997	rat	24-28 mo	0.30 / NA	0.02	100	0.2
Appelman *et al*., 1988	rat	52 wk	9.4 / 1.0	0.06	30	2
Rusch *et al*., 1983	rat	26 wk	2.95 / 0.98	0.2	30	7
Kimbell *et al*., 1997	rat	26 wk	6 / 2	0.1	30	3
Wilmer *et al*., 1989	rat	13 wk	4 / 2	0.2	300	0.7
Woutersen *et al*., 1987	rat	13 wk	9.7 / 1.0	0.03	100	0.3
Zwart *et al*., 1988	rat	13 wk	2.98 / 1.01	0.2	300	0.7
Kerns *et al*., 1983	mouse	24 mo	2.0 / NA	0.05	100	0.5
Maronpot *et al*., 1986	mouse	13 wk	10.1 / 4.08	0.09	100	0.9
Rusch *et al*., 1983	monkey	26 wk	2.95 / 0.98	none	300	4

The most striking observation is the similarity of potential RELs among the rat chronic studies (exposures $\geq$ 26 weeks) that contain a NOAEL. The range of RELs from these animal studies, 2 – 7 $\mu g/m^3$, is comparable to the proposed REL based on a human study. Another related observation is that the NOAEL and LOAEL are similar among all the studies, regardless of exposure duration. The NOAEL and LOAEL are generally in the range of 1-2 mg/m^3 and 2-10 mg/m^3, respectively, with the exception of the study by Kamata *et al*. (1997). These results indicate that the formation of formaldehyde-related nasal lesions are more concentration dependent than time, or dose, dependent.

A limitation of a majority of the occupational studies is their high reliance on surveys and other methods that focus on sensory irritation. Such sensory irritant results, as exhibited in the Wilhelmsson and Holmstrom (1992) study, may be more related to recurrent acute injury rather than a true chronic injury. The concentration dependent nature of the nasal lesions in the supporting animal studies, and suggested in the supporting human nasal biopsy study, would also imply that the nasal cavity endpoint may be a recurrent acute effect. However, Kerns *et al*. (1983) and Kamata *et al*. (1997) clearly demonstrated that near the LOAEL, increasing exposure durations would result in nasal lesions at lower formaldehyde concentrations. Also, the rat study by Woutersen *et al*. (1989) demonstrated that subchronic exposure to formaldehyde concentrations that produce nasal lesions could result in lifelong changes of the nasal epithelium. These findings substantiate the chronic nature of the nasal/upper airway injury that results from long-term formaldehyde exposure.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL include the use of human exposure data from workers exposed over a period of years and the observation of a NOAEL. In addition, a number of well-conducted animal studies supported the derivation of the REL. The major areas of uncertainty are the uncertainty in estimating exposure in the occupational studies and the potential variability in exposure concentration.

VIII. References

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